977 HIGHLY CYTOTOXIC RESILIENT CD8+ T CELLS AVOID EXHAUSTION BY LOWERING ROS THROUGH ME1 UPREGULATION

[1]Joanina Gicobi*, [1]Haidong Dong, [2]Cindy Liu. [1]*Mayo Clinic Graduate School of Biomedical Sciences, Rochester, MN, United States*; [2]*Department of Urology, Mayo Clinic, Rochester, MN, United States*

Background Cytotoxic T cells are indispensable in protecting the organism from malignant disease. Even though they are prone to be exhausted in patients with large tumor burden, some of them can regain their antitumor activity upon immune checkpoint inhibitor (ICI) therapy and reject large tumors or metastatic malignances. Our knowledge to these "rebound" effector T cells is limited. Recently, resilient T cells have been perceived to explain the presence of highly cytotoxic T cells that are less exhausted and rebound in responses to ICI therapy, however the phenotypic and functional characters of resilient T cells have not been clearly defined.

Methods CD8+ T cells were isolated from PBMCs and stained with TMRM. They were then sorted into Low and High Δψm cells. Following activation with or without other experimentation, we conducted killing assays, metabolic assays, flow cytometry, Bulk RNA sequencing, western blot, qPCR etc.

Results We found ICI-therapy responsive CX3CR1$^+$ CD8$^+$ T cells are endowed with low mitochondrial potential (Δψm). The frequency of CX3CR1$^+$ CD8$^+$ T cells with low Δψm increased in patients with metastatic malignances who have better clinical outcomes in responses to ICI therapy and radiation therapy. Further characterization of CD8$^+$ T cells with low Δψm revealed that they are highly cytotoxic and produce less ROS (reactive oxygen species) but express more ME1 (malic enzyme 1). Interestingly, overexpression of ME1 reduced ROS in CD8$^+$ T cells and augmented tumoricidal activity of CD8$^+$ T cells. Importantly, enhanced expression of ME1 in T cells isolated from patients improved cytotoxic T cell responses to ICI treatment in vitro.

Conclusions Our study suggests that not all highly cytotoxic CD8$^+$ T cells are exhausted but some of them are functionally resilient in patients with advanced cancers. Modification of ME1 expression in T cells could be a new method to avoid T cell exhaustion and to improve the efficacy of cancer immunotherapy.

Ethics Approval Study approval. "Healthy Donor" human blood leukocytes were acquired from anonymous donors who had consented for blood donation at the Blood Transfusion Center at Mayo Clinic. All donors and patients provided signed informed written consent; the study was approved by the Mayo Clinic Rochester IRB and was conducted according to Declaration of Helsinki principles.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0977